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Ovarian steroids act as respiratory stimulant and antioxidant against the causes and consequences of sleep-apnea in women

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ABSTRACT

Evidence supports the importance of ovarian hormones as potential tools against sleep apneas in women. On one hand, progesterone is largely acknowledged as being a respiratory stimulant that reduces the frequency of apneas, but the underlying mechanisms remain poorly understood. Recent studies in mice showed that the respiratory effects of progesterone are mediated by at least two classes of progesterone receptors, including the nuclear (nPR) and membrane receptors (mPR). Some of these receptors (nPR) have sex-specific effects on the frequency of apneas recorded during sleep in mice, while mPRβ acts in males as well as in females. Moreover, sleep apnea is a condition that induces an "oxidative stress" response in several tissues, and this contributes to the deleterious consequences of sleep apneas, including the development of hypertension. While estradiol is recognized as an antioxidant hormone, its potential protective role has remained mostly ignored in the field. We will review recent data supporting an antioxidant role of estradiol in female rats exposed to intermittent hypoxia, a reliable animal model of sleep apnea. Since estradiol has two main receptors (ERα and ERβ) we will discuss their relative implications, and present new data showing a key role for ERα to prevent the hypertension induced by intermittent hypoxia. Overall this review highlights the fact that ovarian hormones could potentially be used as efficient tools against the causes (i.e. instabilities of the respiratory control system) and consequences (oxidative stress) of sleep apnea.

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1. Introduction

Sleep-apnea is a chronic health condition characterized by repeated cessations of breathing occurring during sleep. This atypical breathing pattern results in abrupt and repeated variations of arterial oxygen pressure, known as intermittent hypoxia (IH).

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IH induces several pathological responses (hypertension, cognitive impairments, and metabolic disorders), and produces cellular damages mostly linked to exaggerated production and impaired protection against reactive oxygen species (ROS), which are one of the inevitable by-products of cellular O_2 consumption (Almendros et al., 2014; Lavie, 2015; Prabhakar et al., 2015). It is largely acknowledged that sleep apnea is a sex specific disease: its prevalence is higher in men than in premenopausal women (with a men:women ratio of 2:1 to 3:1 – Bixler et al., 2001; Redline et al., 1994) and its occurrence is 3–4 times higher in women after vs before menopause (Bixler et al., 2001; Redline et al., 1994; Young et al., 2003).

It is noteworthy that beyond their roles in reproductive biology, ovarian hormones (estradiol and progesterone) regulate a large variety of homeostatic functions, including the cardio-circulatory (Hay, 2016; Pang et al., 2015), respiratory (Boukari et al., 2015; Dempsey et al., 1986), and metabolic (Shen and Shi, 2015; Stefanska et al., 2015) systems. The fact that progesterone is a respiratory stimulant is largely acknowledged in humans or in animal models (reviewed in Behan and Kinkead, 2011; Boukari et al., 2015; Dempsey et al., 1986). Based on these data, there has been a clinical interest to address the hypothesis that progesterone could reduce the frequency of apneas or airway obstructions during sleep (Pickett et al., 1989; Polo-Kantola et al., 2003; Saaresranta et al., 2006). Population-based studies supported this hypothesis by showing that hormone replacement therapy in postmenopausal women was associated with a lower frequency of sleep apneas, with more potent effects being obtained in women taking both estrogens and medroxyprogesterone, compared to women taking only estrogens (Bixler et al., 2001; Shahar et al., 2003). The roles of these hormones as potential tools against apnea in women was also supported by studies showing an inverse relation between the level of circulating ovarian hormones and apnea frequency in women (Galvan et al., 2017; Netzer et al., 2003).

Hormone replacement therapy for the treatment of menopause symptoms in women has gone through drastic changes over the past 15 years. The preliminary results of the Women's Health Initiative (WHI) study showed an increased risk of coronary heart disease, breast cancer, stroke, and thromboembolic complications in women taking hormones therapy (Rossouw et al., 2002), and therefore, the rate of prescription and use of hormone therapy has fallen drastically. However, these data should have been stratified by age and time since menopause at the initiation of treatment, and recent reports suggest that the decreased rate of prescription may have had harmful effects in women (Lobo et al., 2016). It is now clear that starting hormone therapy within 10 years of menopause has more benefits than risks (Bassuk and Manson, 2016; Hodis et al., 2016). In terms of apnea frequency, a recent study showed that following the reduced treatment rate, the effect of hormone therapy on apnea frequency is no longer apparent (Mirer et al., 2015). This could be due to the prescription of lower doses of hormones for the treatment of menopausal symptoms, or to a "healhty user bias": before the results of the WHI study, hormone therapy was perceived as a healthy habit, and a high proportion of women taking hormone therapy had a healthier life-style than women not taking medication (Mirer et al., 2015). Finally, the authors suggested that the biological basis of the effects of ovarian hormones on breathing during sleep should be questioned, and that hormone therapy is unlikely to benefit sleep health in postmenopausal women.

On the contrary, there are clear-cut and consistent evidence from humans and animal models that progesterone is a powerful respiratory stimulant (see for review Behan and Kinkead, 2011; Boukari et al., 2015; Dempsey et al., 1986). Despite this large knowledge, several aspects of the precise functions and mechanisms explaining the respiratory effects of sex hormones remain to be clarified. In this review, we will discuss two major points, which are key aspects suggesting potential avenues for the treatment of respiratory disorders during sleep in women. We believe that these should be taken into consideration for future development in this field.

- It is becoming clear that the mechanisms by which progesterone stimulates the respiratory system are far more complex than initially thought. There are now 8 identified progesterone receptors: the nuclear progesterone receptor (nPR), 5 members of membrane progesterone receptors family (mPR), and at least 2 members of the Progesterone receptormembrane component family (Pgrmc) (Brinton et al., 2008; Pang et al., 2013; Petersen et al., 2013). Their relative roles on respiratory control are only partially known. Future research should identify which progesterone receptors are involved in respiratory control and the occurrence of apnea during sleep, which ultimately could help developing more specific drugs.
- Sleep apnea is an oxidative stress disorder: most of its consequences are thought to be due to an imbalance between the generation and clearance of reactive oxygen species in different tissues, including the central and peripheral nervous system, the liver, or the circulatory system (Almendros et al., 2014; Lavie, 2015; Prabhakar et al., 2015; Quintero et al., 2013). Estradiol and progesterone are well known for their anti-oxidant functions, and we should ask how relevant this is for the development or treatment of sleep apnea in women.

One should keep in mind that an important drawback of the sex-specific occurrence of sleep-apnea is that women are largely under-represented in sleep apnea clinics and research protocols: in a population-based survey including 389 participants (16–84 years of age) 38% of men and 15% of women had sleep-apneas, (men:women ratio = 2.5:1), but in the same population, the men:women ratio referred for clinical evaluation of sleep apneas was 8:1 (Redline et al., 1994). On this background, the Society for Women's Health recently recommended the use of animal models to better understand sex-specific sleep disorders (Mallampalli and Carter, 2014). Our current studies are in line with these recommendations: we are using animal models to better understand the effects of progesterone and estradiol as tools acting both as respiratory stimulants and antioxidant agents, therefore modulating both the causes, and the consequences of sleep apnea.

2. A complex network of progesterone receptors likely involved in respiratory control

Progesterone exerts its physiological functions by binding and activating several specific receptors. We have recently reviewed this topic (Boukari et al., 2015; Joseph et al., 2013), and provided data supporting the hypothesis that the respiratory effects of progesterone are mediated by the classic nuclear receptors (Marcouiller et al., 2014), but also by membrane progesterone receptors (Boukari et al., 2016).

2.1. Role of nuclear progesterone receptor in respiratory control and apnea frequency

Several isoforms of the nPR can be synthetized by alternative splicing of a common gene, among these nPR-A and nPR-B are transcription factors regulating gene expression in presence of their ligands and coactivators (Camacho-Arroyo et al., 2007; Gonzalez-Flores et al., 2011). nPRs are present in brain areas involved in respiratory control such as brainstem and hypothalamic nuclei, at the middle and caudal levels of the nucleus tractus solitarius (NTS